31. (Thrice Amended) A neutral lipid oligonucleotide association comprising a neutral lipid associated with an antisense oligonucleotide of from about 8 to about 50 bases and complementary to [at least 8 bases of] the translation initiation site of Bcl-2 mRNA, wherein said translation initiation site comprises the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

52. (Twice Amended) A composition comprising a first antisense polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a primary phosphatide associated with said first polynucleotide, wherein said primary phosphatide is a neutral lipid, and wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1), and wherein said polynucleotide is complementary to the translation initiation site of Bcl-2.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1, 9, 31 and 52 have been amended. Claims 1-41, 43-50 and 52-56 are therefore pending.

For the convenience of the Examiner, a copy of the pending claims is attached hereto as **Exhibit A**.

B. Support for the Claims

Claims 1, 9, 31 and 52 have revised to clarify the polynucleotide as an antisense polynucleotide that is complementary to the Bcl translation initiation site. Support for this amendment can be found throughout the specification as filed, at least at pageS 10-11.

In light of the foregoing information, it will be understood that no new matter is included within any of the amended claims.

C. The Rejection of Claims 1-3, 5-9, 31, 33-42 and 47-55 Under 35 U.S.C. § 112, First Paragraph Is Overcome

The Action has rejected claims 1-3, 5-9, 31, 33-42 and 47-55 under 35 U.S.C. § 112, first paragraph, as not meeting the "written description" requirement.

Applicants respectfully traverse. The presently claimed invention meets the written description requirement of 35 U.S.C. § 112, first paragraph.

The Action argues that the 8 nucleotides of SEQ ID NO:1 may comprise nucleotides in any order. Applicants submit that the term "hybridizes" in the instant claims clarifies that the polynucleotide sequence must be sufficiently complementary to the target polynucleotide sequence to bind it. Applicants submit that this would be understood by one of ordinary skill in the art in light of the specification and claims.

However, to remove issues for appeal, Applicants hereby elect to amend claims 1, 9, 31 and 52 to specify that the polynucleotide is an "antisense" polynucleotide that is "complementary" to the Bcl translation initiation site. These embodiments are described at pages 10-11.

> Targeting double-stranded (ds) DNA with polynucleotides leads to triple-helix formation; targeting RNA will lead to double-helix formation. Antisense polynucleotides, when introduced into a target cell, specifically bind to their target polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene transcription or translation or both within a host cell, either *in vitro* or *in vivo*, such as within a host animal, including a human subject.
>
> As used herein, the terms "complementary" or "antisense" mean polynucleotides that are substantially complementary over their entire length and have very few base mismatches. For example, sequences of fifteen bases in length may be termed complementary when they have a complementary nucleotide for thirteen or fourteen positions out of fifteen. Naturally, sequences which are "completely complementary" will be sequences which are entirely complementary throughout their entire length and have no base mismatches.

> Other sequences with lower degrees of homology also are contemplated. For example, an antisense construct which has limited regions of high homology, but also contains a non-homologous region (*e.g.*, a ribozyme) could be designed. These molecules, though having less than 50% homology, would bind to target sequences under appropriate conditions.

As shown in the passages above, the term "antisense" refers to polynucleotides that bind to a target "polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability." Target polynucleotides include both DNA and RNA. The terms "antisense" and "complementary" refer to molecules that have "less than 50% homology, and bind to target sequences". As stated at page 11:

> **'Complementary' polynucleotides are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules.** (Emphasis added).

Applicants submit that one of skill in the art would understand the meaning of these terms, and would be able to design antisense or complementary polynucleotides that comprise eight nucleotides of SEQ ID NO:1 so that it would bind the target Bcl transcription initiation region in either a DNA and or RNA target polynucleotide. Applicants submit that the claims are clear as to their meaning when read in light of the specification by one of ordinary skill in the art, and respectfully request that this rejection be withdrawn.

D. The Rejection of Claims 1-9, 31-37, 39-41, 48-50, 52-54 and 56 Under 35 U.S.C. § 103(a) Over Evan or Reed or Green *et al.* in view of Tari *et al.* Is Overcome

Claims 1-9, 31-37, 39-41, 48-50, 52-54 and new claim 56 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Evan (WO 93/20200) or Reed (WO 95/08350) or Green *et al.* (U.S. Patent No. 5,583,034) in view of Tari *et al.* (U.S. Patent No. 5,417,978). The Office maintains the rejection made in the previous Action mailed January 4, 1999.

Applicants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

The Action has admitted at page 5 that Evan or Reed or Green *et al.* do not teach a liposome made of neutral lipids. Applicants respectfully submits that the Office, in its argument to provide the motivation to combine Tari *et al.* with the other cited references, has incorrectly characterized Tari *et al.* Applicants find that Tari *et al.* does not provide guidance to specifically select a neutral lipid based on these properties. Tari *et al.* teaches that these properties are common to all liposome constructs (*i.e.* "the invention' of the Tari *et al.* reference), at column 2, lines 49-56:

> The advantages of **the invention** include improved stability of the antisense oligonucleotides compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhanced specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions in which similar gene rearrangements are observed. (Emphasis added).

The invention of Tari *et al.*, is defined at column 1, line 65 to column 2, line 3:

> The present invention relates to a liposomal methyl phosphonate oligonucleotide composition. The composition comprises (a) a liposome which comprises at least one phospholipid, and (b) an antisense methyl phosphonate oligonucleotide which is entrapped in the liposome.

Applicants submit that the broad teaching of the general advantages of a phospholipid liposome and an antisense methyl phosphonate oligonucleotide, the invention of the Tari *et al.* reference, (column 1, line 66 to column 2, line 3) is not a teaching, suggestion or guidance of the neutral lipid and antisense Bcl-2 oligonucleotide composition of the presently claimed invention (*i.e.* the invention of the rejected claims). The advantages referred to by the Action are disclosed in regards to all liposome constructs described by Tari *et al.*, without a teaching, suggestion or guidance to use either charged or neutral lipids, let alone specifying the lipid

dioleolphosphatidylcholine. Thus, this teaching does not provide the necessary guidance to a neutral lipid to combine this reference with the other cited references.

The teachings of Tari *et al.*, including the teachings of the benefits of a charged lipid, must be considered as a whole in the evaluation of the obviousness or non-obviousness of the claimed invention, as stated in the MPEP at 2141.02:

> A prior art reference must be considered in its entirely, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

Applicants submit that Tari *et al.* demonstrates that both neutral and charged lipids incorporates oligonucleotides, and that the tested charged lipid does so better than most of the uncharged lipids tested, including dioleoyl (C18:1) phosphatidylcholine. At column 6, Table 4, Tari *et al.* shows a working example where an equal or greater incorporation of oligonucleotides in a charged lipid construct (*i.e.* dioleoyl (C18:1) phosphatidylserine) when compared to dioleoyl (C18:1) phosphatidylcholine ("DOPC") and the majority of uncharged lipid constructs. Applicants submit that this teaching may indicate that charged lipid constructs may be more therapeutically effective than an uncharged liposome construct, as a charged liposome contains as much or more oligonucleotides as most of the uncharged lipids.

Applicants submit that there is a difference in the motivation for selecting a type of lipid that has a property of ease of handling in an experimental setting and the motivation for selecting the type of lipid that has a property of high uptake of oligonucleotides. The latter property would be attractive to gain the maximum therapeutic benefit via delivery of oligonucleotides. Because the claimed invention relates to compositions and methods of delivery of polynucleotides to hybridize to the Bcl-2 gene, *i.e.* in therapeutic applications, a higher uptake of oligonucleotides

would be the desirable property. And this desirable property is possessed by the charged lipid example more so than the majority of uncharged lipids, including DOPC. Applicants also note that Tari *et al.* indicates that other lipids tested were easy to handle, but did not exclude charged lipids from having this property (see column 6, lines 53-54). Because the teachings of Tari *et al.* demonstrates desirable properties in both uncharged and charged lipids, this reference does not provide motivation for specifically selecting uncharged lipids from the teachings of charged and uncharged lipids for combining with the other cited references.

Further, Applicants again respectfully submit that the Office has not properly considered the previously submitted declaration of Drs. Tari and Lopez-Berestein (attached as Exhibit B) in its evaluation of obviousness or non-obviousness of the claimed invention in light of the cited art. The Office "should consider all rebuttal arguments and evidence presented by applicants" *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), MPEP 2144.08 B. Applicants declaration demonstrates the surprising and unexpected properties of the claimed invention over the teachings of the cited references, and should be given substantive weight, as described in the MPEP at 2144.08 B:

> However, to be entitled to substantial weight, the applicant should establish a nexus between the rebuttal evidence and the claimed invention, *i.e.* objective evidence of nonobviousness must be attributable to the **claimed invention**. (Emphasis added)

Applicants contend that all relevant prior art teachings must be considered in evaluation of obviousness (See MPEP 2144.08(II)(A)(4)). Tari *et al.* teaches, at column 2, lines 53-55, "an enhanced **specific** therapeutic effect of the antisense oligonucleotides" (emphasis added) of its invention, which includes both charged and uncharged liposomal constructs. The data presented in this declaration demonstrates that charged liposomes are non-specifically toxic to the tested

cell lines. This data is surprising and unexpected because it demonstrates the advantage of the presently claimed invention over the charged and uncharged liposomes taught in Tari *et al.*

Applicants contend in light of the full teachings of the benefits of both neutral and charged liposomes by Tari *et al.*, the evidence of surprising and unexpected advantages associated with the use of antisense Bcl-2 oligonucleotides associated specifically with neutral lipids rebuts any asserted *prima facie* case of obviousness:

> One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected [because] that which would have been surprising would not have been obvious. The principle applies most often to predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

In light of the forgoing, Applicants respectfully request that this rejection be withdrawn.

E. The Rejection of Claims 1-8, 10-36, 39, 44, 46, 48-50, 52-54 and 56 Under 35 U.S.C. § 103(a) Over Abukarkr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* Is Overcome

Claims 1-8, 10-36, 39, 44, 46, 48-50, 52-54 and new claim 56 are rejected under 35 U.S.C. § 103(a) over Abubakr *et al.* (*Blood* 82 (10 Suppl. 1) 374a, Abstract #1481), Pocock *et al.* (*Blood* 82 (10 Suppl. 1, 200A, Abstract #784) and Cotter *et al.* (*Oncogene*, 9:3049-3055, 1994) as allegedly being obvious in view of Tari *et al.* (U.S. Patent No. 5,417,978).

Applicants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

The Action has admitted that Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*, do not teach "administration of the antisense oligonucleotide as a composition comprising neutral lipids." The Action again relies on the teachings of Tari *et al.* to provide the motivation for combining

the teachings of all these references. As with the rejection of the claims described above in section D of this paper, Applicants respectfully submit that the Office, in its arguments for the motivation to combine Tari *et al.* with the other cited references, has incorrectly characterized Tari *et al.* The Action states that one of ordinary skill in the art would be "motivated by the teaching of Tari *et al.* that the neutral lipid composition impart several benefits." Tari *et al.* instead teaches that these properties are common to all liposome constructs, at column 2, lines 49-56. Applicants further find, as previously described in section D of this paper, that Tari *et al.* teaches the benefits of a charged lipid as having a high oligonucleotide uptake property. Thus, the benefits of both charged and uncharged liposomes are taught by Tari *et al.*, and one of skill in the art would not be lead to select only neutral lipids based on the teachings of Tari *et al.*

Applicants respectfully request that this rejection be withdrawn.

REMARKS

The Examiner is invited to contact the undersigned attorney at (512) 418-5601 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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